



Cardioprotective Role of *Malus domestica* Peel Phytochemicals in Myocardial Infarction: A Review

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ABSTRACT :

Myocardial infarction is a major cardiovascular disorder associated with inadequate coronary blood flow and progressive myocardial injury. Ischemia and subsequent reperfusion can cause oxidative stress, calcium overload, mitochondrial dysfunction, inflammation, and cardiomyocyte death. Excessive generation of reactive oxygen species further aggravates cellular damage and disturbs normal cardiac function.

Malus domestica (apple) is a rich source of biologically active compounds, with the peel containing considerable amounts of phenolics, flavonoids, anthocyanins, and other phytoconstituents. Compounds such as quercetin, catechins, phloridzin, isoquercitrin, and ursolic acid have been reported to possess antioxidant and anti-inflammatory activities.

The reviewed evidence suggests that these constituents may help reduce oxidative stress, regulate inflammatory signaling, and support mitochondrial function.

Overall, the available literature indicates that the combined action of apple peel phytochemicals may contribute to protection against myocardial damage.

Introduction

Cardiovascular diseases are among the leading causes of death worldwide and continue to pose a serious challenge to public health. Ischemic heart disease represents a major form of cardiovascular disease and occurs when the myocardium does not receive an adequate supply of blood and oxygen. One of its severe clinical manifestations is myocardial infarction (MI), which develops when coronary blood flow is markedly reduced or completely interrupted. Coronary artery blockage, commonly associated with thrombus formation, restricts the delivery of oxygen and nutrients to cardiac tissue. If the ischemic condition persists, progressive damage to the myocardium may occur, resulting in impaired cardiac function and, in severe cases, heart failure or death (Zhang et al., 2022).

Myocardial infarction (MI) continues to be a significant health concern because of its high contribution to illness and death worldwide. The occurrence of MI can have a considerable effect on patients as well as healthcare services, particularly because cardiac injury may affect long-term health and daily functioning. This emphasizes the importance of developing effective approaches for reducing myocardial damage, improving clinical outcomes, and supporting the quality of life of affected individuals (Sachdeva et al., 2023).

Acute myocardial infarction (AMI) remains a major cause of mortality worldwide, with millions of deaths reported annually. Myocardial reperfusion injury develops when restoration of blood flow to the ischemic myocardium is accompanied by additional cellular stress and damage. Several interrelated factors contribute to this process, including excessive oxidative stress, intracellular calcium accumulation, impaired mitochondrial function, metabolic imbalance, and changes in cellular signaling. Together, these disturbances can initiate inflammatory responses and promote cardiomyocyte injury and cell death. Among these mechanisms, excessive ROS generation and the resulting oxidative stress play an important role in the progression of myocardial damage (Villa et al., 2025).

Oxidative and nitrosative stress are important contributors to myocardial injury during MI. Excessive generation of ROS and RNS can impair cardiomyocyte function and promote tissue damage. In cardiac tissue, these reactive species arise from several sources, including mitochondria, NADPH oxidase, nitric oxide synthase, xanthine oxidase, and lipoxygenase/cyclooxygenase systems. Excessive ROS production may contribute to the development and progression of atherosclerotic lesions by promoting LDL oxidation and activating matrix metalloproteinases. These changes can weaken the atherosclerotic plaque and increase the possibility of plaque rupture, which may subsequently lead to coronary artery blockage and myocardial infarction. Therefore, antioxidant approaches, including flavonoids, may provide cardioprotection by limiting ROS-mediated damage and lipid peroxidation (Ismail et al., 2025).

Malus domestica Borkh., commonly known as apple, belongs to the Rosaceae family and is widely cultivated as a fruit crop. It is also recognized as a rich source of diverse biologically active compounds. Its phytochemical profile comprises polyphenols, phenolic acids, flavonoids, phytosterols, triterpenoids, pectin, and other nutritional constituents. Among these, chlorogenic, caffeic, ferulic, and p-coumaric acids, along with flavonoids such as catechin, epicatechin, quercetin, and anthocyanins, are important bioactive compounds. These constituents are present in both the pulp and peel and have been associated with antioxidant and anti-inflammatory properties (Patocka et al., 2020).

Molecular Pathogenesis of Myocardial Infarction

1. Coronary Artery Obstruction and Myocardial Ischemia

Prolonged reduction in coronary blood flow deprives the myocardium of oxygen and nutrients. Persistent ischemia can cause irreversible cardiomyocyte injury and necrosis, while early restoration of blood flow may preserve viable myocardium (Skyschally et al., 2008).

2. Atherosclerosis and Endothelial Dysfunction

Reduced nitric oxide (NO) availability impairs endothelial function and promotes vascular dysfunction. ROS can further reduce NO through peroxynitrite formation. Atherosclerosis involves lipid accumulation and chronic inflammation within the arterial wall and may lead to coronary artery obstruction. Reperfusion can additionally increase ROS and RNS production, causing oxidative and inflammatory damage.

3. Ischemia-Induced Metabolic and Ionic Changes

Oxygen deficiency shifts cardiac metabolism toward anaerobic glycolysis, reducing ATP and increasing lactate. ATP depletion disturbs ion transport and contributes to Na^+ and Ca^{2+} accumulation. Altered calcium handling can impair contraction and mitochondrial function (Zuber et al., 2024).

4. Intracellular Na^+ Accumulation

Ischemic acidosis activates the Na^+/H^+ exchanger, causing increased Na^+ entry into cardiomyocytes. Reduced Na^+/K^+ -ATPase activity due to ATP depletion can further increase intracellular Na^+ .

5. Intracellular Ca^{2+} Accumulation

Increased intracellular Na^+ promotes reverse $\text{Na}^+/\text{Ca}^{2+}$ exchange, resulting in Ca^{2+} accumulation inside cardiomyocytes. This calcium overload contributes to cellular and mitochondrial injury.

6. Mitochondrial Ca^{2+} Accumulation

Excess cytosolic Ca^{2+} is taken up by mitochondria, producing mitochondrial Ca^{2+} overload and swelling. ATP depletion and Ca^{2+} accumulation can promote contracture and progressive cardiomyocyte injury.

7. Reperfusion-Associated Ca^{2+} Overload

Rapid correction of extracellular pH during reperfusion activates the Na^+/H^+ exchanger and reverse $\text{Na}^+/\text{Ca}^{2+}$ exchange. This increases intracellular Ca^{2+} and may promote hypercontracture, MPTP opening, and mitochondrial injury (Webster et al., 2012).

8. Mitochondrial Dysfunction and Oxidative Stress

Mitochondria produce ATP and are important sources of ROS, mainly through respiratory Complexes I and III. Excess ROS can damage proteins, lipids, and DNA and promote MPTP opening. The resulting mitochondrial dysfunction may generate further ROS, creating a cycle of cellular injury (Peoples et al., 2019).

9. Oxidative Stress and Mitochondrial ROS

During ischemia–reperfusion, ROS may arise from mitochondrial Complexes I and III, xanthine oxidoreductase, uncoupled nitric oxide synthase, and NOX2/NOX4. Excess ROS can disturb Ca^{2+} handling, promote lipid peroxidation, and contribute to cardiomyocyte death.

10. Reperfusion Injury

Although reperfusion restores oxygen supply, it can produce additional myocardial damage. Excess ROS, Ca^{2+} overload, MPTP opening, and inflammation contribute to mitochondrial dysfunction and cardiomyocyte injury. Reperfusion may also cause myocardial stunning, arrhythmias, and microvascular no-reflow.

11. Early ROS Generation

The early stage of reperfusion is associated with rapid ROS production, particularly from mitochondrial Complexes I and III. Other enzymatic sources include xanthine oxidoreductase, uncoupled nitric oxide synthase, and NADPH oxidases. Increased ROS can promote oxidative damage and ferroptosis.

12. Reperfusion-Associated Ca^{2+} Overload

Reperfusion increases intracellular Ca^{2+} through altered Na^+/H^+ and $\text{Na}^+/\text{Ca}^{2+}$ exchange. Ca^{2+} overload can cause hypercontracture, MPTP opening, loss of mitochondrial membrane potential, and release of apoptotic mediators.

13. pH Paradox and Inflammation

During ischemia, intracellular acidosis helps keep the MPTP relatively closed. Rapid pH recovery during reperfusion may promote pore opening and mitochondrial dysfunction. Reperfusion also activates inflammatory pathways involving neutrophils, NF- κ B, and the NLRP3 inflammasome.

14. Interaction of ROS, Ca^{2+} and Mitochondria

ROS and Ca^{2+} overload reinforce each other during myocardial injury. Excess Ca^{2+} uptake by mitochondria can cause MPTP opening, loss of membrane potential, reduced ATP production, and release of apoptotic factors. Mitochondrial damage can then increase ROS generation further (Morales-Carreno et al., 2022).

15. Mitochondrial Membrane Changes and Cell Death

Ca²⁺ overload and oxidative stress can alter mitochondrial membrane permeability and activate different cell-death pathways. MPTP opening mainly contributes to necrotic injury, whereas MOMP facilitates apoptosis through release of mitochondrial apoptotic factors. Apoptosis, necrosis, and autophagy may overlap during ischemia–reperfusion. Therefore, mitochondrial pathways such as MPTP and MOMP are important targets for limiting cardiomyocyte loss (**Webster et al., 2012**).

Phytochemical Profile of Apple Peel

Apple contains a wide range of flavonoids and phenolic compounds, although their levels vary with cultivar, harvesting, storage, processing, and plant part. Reported constituents include quercetin glycosides, catechin, epicatechin, procyanidins, cyanidin-3-galactoside, p-coumaric acid, chlorogenic acid, gallic acid, phloridzin, phloretin glycosides, and vitamin C. Their distribution differs between peel and flesh, with the peel generally being richer in phenolics and flavonoids, particularly quercetin, procyanidins, catechin, epicatechin, and phloridzin. In contrast, chlorogenic acid is generally more concentrated in the flesh. Overall, apple peel may contain approximately 2–6 times higher phenolic content and 2–3 times higher flavonoid content than the flesh, depending on the cultivar (**Patel et al., 2012**).

Apple peel is a concentrated source of phenolic compounds and antioxidants, generally containing higher levels of these constituents than the edible flesh. Important phytochemicals reported in the peel include procyanidins, chlorogenic acids, flavonoids, hydroxycinnamic acids, anthocyanins, and quercetin derivatives. These constituents are considered important contributors to the antioxidant capacity of apple peel and have been associated with several biological activities, including antihypertensive, antidiabetic, anti-inflammatory, and antiproliferative effects.

Red-skinned apple cultivars are particularly notable for their anthocyanin content, which contributes to the characteristic red colour of the peel. Carotenoids are also present, while the overall phytochemical profile of apple peel can vary depending on cultivar, maturity, environmental conditions, harvesting, storage, and processing practices (**Vasile et al., 2021**).

A. Polyphenols

Apple contains several classes of polyphenols, mainly phenolic acids, dihydrochalcones, and flavonoids. Chlorogenic and caffeic acids are important phenolic acids, while phloridzin, phloretin, and phloretin-2-xyloglucoside represent major dihydrochalcones. Important flavonoids include catechin, epicatechin, proanthocyanidins, quercetin, and quercitrin. Other reported phenolics include gallic acid, protocatechuic acid, ferulic acid, p-coumaric acid, and myricetin. Their distribution varies among cultivars and fruit tissues, with the peel generally containing greater amounts than the pulp. Quercetin glycosides are mainly concentrated in the peel, whereas cyanidin-3-galactoside is particularly associated with red apple peel. These compounds contribute substantially to the antioxidant and anti-inflammatory properties of apple.

Apple polyphenols have also been associated with diverse biological activities, including hepatoprotective, anti-inflammatory, antibacterial, anticancer, antidiabetic, anti-obesity, and cardioprotective effects. They may help regulate oxidative stress, lipid metabolism, endothelial function, and inflammatory responses. The higher phenolic and flavonoid content of the peel may contribute to its greater biological activity compared with the flesh. Among the major polyphenolic groups are procyanidins, anthocyanins, hydroxycinnamic acids, dihydrochalcones, flavonols, and flavan-3-ols. Dihydrochalcones such as phloretin and phloridzin have been reported to possess antioxidant, antidiabetic, anti-inflammatory, antimicrobial, anticancer, and anti-obesity activities. Apple also contains ursolic acid, a pentacyclic triterpenoid reported to exhibit antioxidant, anti-inflammatory, hepatoprotective, anti-atherosclerotic, cardiovascular, and other biological activities.

B. Polysaccharides (Pectin)

Apple is an important source of dietary polysaccharides, particularly pectin. Its structure is composed mainly of polygalacturonic acid with side chains containing sugars such as arabinose, galactose, and rhamnose. Apple pectin functions as dietary fibre and possesses gelling and emulsifying properties. The peel generally contains more dietary fibre than the pulp. Pectin has been associated with cholesterol-lowering, lipid-regulating, digestive, anti-obesity, and anticancer effects and may also support the intestinal availability of beneficial phytochemicals.

C. Phytosterols

Apple contains phytosterols such as β -sitosterol, stigmasterol, campesterol, and daucosterol, which are mainly associated with plant cell membranes. These compounds have been reported to possess antioxidant, anti-inflammatory, hypocholesterolemic, cardioprotective, and wound-healing properties. Their ability to influence cholesterol absorption and metabolism may contribute to their potential role in cardiovascular and other chronic diseases.

D. Pentacyclic Triterpenes

Apple peel is a notable source of pentacyclic triterpenes, including ursolic acid, oleanolic acid, maslinic acid, and related derivatives. These compounds exhibit diverse biological activities, particularly anticancer and antiproliferative effects. Ursolic acid and related triterpenes have also been associated with anti-inflammatory, antioxidant, and muscle-protective activities. Thus, pentacyclic triterpenes represent an important group of bioactive constituents of apple peel with considerable therapeutic potential (**Patocka et al., 2020**).

E. Anthocyanins

Anthocyanins are flavonoid pigments derived from flavylium-based structures and are particularly abundant in red-coloured apple peels. They have been reported to exhibit antioxidant, antihyperlipidemic, antihyperglycemic, cardiovascular, neuroprotective, and blood pressure-lowering effects. Their antioxidant and cardioprotective properties suggest a potential role in limiting oxidative damage and supporting cardiovascular health. Anthocyanins have also been investigated for their possible protective effects in conditions such as Alzheimer's disease and diabetic retinopathy (**Jana et al., 2017**).

F. Quercetin

Quercetin is a naturally occurring flavonol found in several foods, including apples, onions, berries, grapes, tea, cereals, broccoli, and cherries. It possesses diverse biological activities, including antioxidant, neuroprotective, antidiabetic, hepatoprotective, and cardioprotective effects. Quercetin has

been reported to enhance NRF2-mediated antioxidant defense, thereby helping to counter oxidative stress and cellular injury. Its protective effects have also been associated with modulation of antioxidant and inflammatory pathways, particularly those involving NRF2.

G. Ursolic Acid

Ursolic acid is a pentacyclic triterpenoid found in apples, fruit peels, berries, basil, and several medicinal plants. It has been reported to exhibit antioxidant, anti-inflammatory, anticancer, neuroprotective, and hepatoprotective activities. Its biological effects are associated in part with modulation of the NRF2 signaling pathway and regulation of oxidative stress and inflammation. Studies have also described its effects on TLR4/NF- κ B and NRF2/ARE pathways in different experimental models.

H. Isoquercitrin

Isoquercitrin isolated from Green Ball apple peel demonstrated anti-inflammatory activity in LPS-stimulated RAW 264.7 macrophage cells. It was reported to decrease the production of inflammatory mediators, including nitric oxide (NO), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), and COX-2, along with suppression of NF- κ B p65. Isoquercitrin also reduced the expression of TNF- α , IL-1 β , IL-6, MCP-1, and PTGES2 in a concentration-dependent manner, indicating its potential as a natural anti-inflammatory constituent of apple peel (Lee et al., 2022).

I. Phloridzin

Phloridzin, also known as phlorizoside or phlorrhizin, is a flavonoid O-glycoside belonging to the dihydrochalcone class. It is mainly found in plants of the *Malus* genus and is an important bioactive constituent of apples. Phloridzin has been reported to influence glucose metabolism through inhibition of intestinal SGLT1-mediated glucose uptake and renal SGLT2-mediated glucose reabsorption. It also exhibits antioxidant activity through free-radical scavenging, inhibition of lipid peroxidation, and enhancement of antioxidant defenses. Studies have further associated phloridzin with anti-inflammatory and cardioprotective effects, including potential protection against diabetic cardiomyopathy and ischemia-related cardiac injury (Tian et al., 2021).

Molecular Mechanism of Cardioprotection

The cardioprotective effects of apple peel and its bioactive constituents may involve multiple interconnected molecular mechanisms, particularly the regulation of oxidative stress, inflammation, antioxidant defense, mitochondrial function, and cell death pathways. Phenolic compounds such as quercetin, phloridzin, catechins, and other flavonoids may contribute to these protective effects through modulation of cellular signaling pathways involved in myocardial injury.

1. Activation of the Nrf2/ARE Antioxidant Pathway

Oxidative stress is an important contributor to myocardial injury, and the Nrf2/ARE pathway represents a major endogenous defense mechanism. Under basal conditions, Nrf2 is retained in the cytoplasm through its interaction with Keap1. During oxidative stress, Nrf2 dissociates from Keap1 and translocates into the nucleus, where it binds to antioxidant response elements (AREs) and promotes the expression of antioxidant and cytoprotective genes, including HO-1, GST, and GCL. Activation of this pathway enhances cellular antioxidant capacity and helps limit oxidative damage in cardiomyocytes (Mohamed et al., 2021).

Several apple-derived compounds have been associated with Nrf2-mediated antioxidant protection. Quercetin has been reported to increase Nrf2 activity and antioxidant enzymes such as SOD, CAT, and GPX, thereby reducing ROS generation and lipid peroxidation. Ursolic acid has also been associated with activation of Nrf2-related signaling and enhancement of cellular antioxidant defense (Thiruvengadam et al., 2021). Thus, stimulation of the Nrf2/ARE pathway may represent an important mechanism through which apple phytoconstituents counter oxidative myocardial injury.

2. Reduction of Oxidative Stress and ROS

Excessive production of reactive oxygen species (ROS) can damage cellular lipids, proteins, and other cellular components and contribute to myocardial dysfunction. Apple is rich in phenolic compounds and flavonoids, including quercetin, catechins, chlorogenic acids, and phloridzin, which possess antioxidant properties. These compounds can contribute to antioxidant defense by reducing oxidative stress and limiting lipid peroxidation. Catechins have also been associated with improved antioxidant defense, reduced ROS, and maintenance of mitochondrial function (Ferenczyová et al., 2021). Therefore, attenuation of ROS-mediated injury may help preserve cardiomyocyte integrity during myocardial stress.

3. Suppression of Inflammatory Signaling

Oxidative stress and inflammation are closely interconnected during myocardial injury. Apple-derived compounds may attenuate inflammatory responses by modulating pathways such as NF- κ B. Phloridzin has been reported to reduce cardiac inflammation and fibrosis through inhibition of the NF- κ B/MyD88 signaling pathway, thereby limiting the release of inflammatory mediators (Xie et al., 2024). Ursolic acid has also been associated with suppression of TLR4/NF- κ B signaling and reduction of inflammatory mediators such as TNF- α , PGE2, and iNOS (Thiruvengadam et al., 2021). In addition, isoquercitrin from apple peel has been reported to suppress NF- κ B-related inflammatory responses and reduce mediators including NO, PGE2, iNOS, COX-2, TNF- α , IL-1 β , and IL-6 (Lee et al., 2022). These effects may reduce inflammation-associated myocardial damage.

4. Protection of Mitochondrial Function

Mitochondria are important targets of oxidative injury in cardiomyocytes because excessive ROS can impair mitochondrial function and energy metabolism. Catechins have been associated with improved mitochondrial function and enhanced antioxidant defense (Ferenczyová et al., 2021). By reducing oxidative stress and maintaining mitochondrial integrity, apple-derived antioxidants may help preserve cellular energy production and reduce downstream oxidative damage.

5. Regulation of Ferroptosis and Cell Injury

Ferroptosis is an oxidative form of regulated cell death associated with lipid peroxidation and impaired cellular antioxidant defense. Evidence from experimental studies indicates that phloridzin may influence this pathway through Nrf2 activation and increased expression of the ferroptosis-related protein SLC7A11. In cardiac models, phloridzin was associated with reduced inflammation and oxidative stress, suggesting a possible role in limiting myocardial injury through modulation of ferroptosis-related mechanisms (Xie et al., 2024).

6. Overall Cardioprotective Mechanism

Collectively, the available evidence suggests that apple peel phytoconstituents may exert cardioprotective effects through interconnected mechanisms. Activation of the Nrf2/ARE pathway enhances endogenous antioxidant defenses, resulting in reduced ROS accumulation and lipid peroxidation. Concurrent suppression of TLR4/NF- κ B and NF- κ B/MyD88 signaling may reduce inflammatory mediator release. These effects can help preserve mitochondrial function, while modulation of Nrf2/SLC7A11-related pathways may contribute to the regulation of oxidative cell death such as ferroptosis. Together, these molecular actions may reduce oxidative and inflammatory myocardial injury and thereby contribute to cardioprotection.

Conclusion

Malus domestica peel represents a promising plant-derived source of phenolic compounds, flavonoids, anthocyanins, and other bioactive constituents. The literature reviewed in this study indicates that compounds such as quercetin, phloridzin, catechins, isoquercitrin, and ursolic acid possess antioxidant and anti-inflammatory properties that may be relevant to cardiovascular protection. Their reported effects on oxidative stress, inflammatory signaling, antioxidant defense, mitochondrial function, and cellular survival provide a possible basis for the cardioprotective potential of apple peel.

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